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Influence of target hemoglobin in dialysis patients on morbidity and mortality

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Influence of target hemoglobin in dialysis patients on morbidity and mortality. Since the introduction of recombinant human erythropoietin (rHuEPO) in 1989, the level of anemia correction has been debated. Information developed from clinical trials and observational studies have given conflicting results. The normal hematocrit (Hct) trial of Besarab et al showed no benefit, and a possible risk, of correcting the Hct from 30% to 42% in hemodialysis patients with NYHA class I to III cardiac disease. The study of Moreno et al in non-cardiac patients showed improved Sickness Impact Profile and Karnofsky scores in hemodialysis patients when their Hct was increased from 31% to 38.5%. Hospitalizations were significantly reduced. Observational studies from Madore et al, Xia et al, Ma et al, and Collins et al all show that increased morbidity and mortality are significantly associated with Hct <33%. Recent data on incident hemodialysis patients indicate the associated risk of death was not different for patients with Hct 33 to <36% versus Hct 36 to <39%. Hospitalization risks and associated costs were significantly less in the patients with Hct 36 to <39%, suggesting that higher Hct values may be less of a concern than previously considered. The current data suggest that patents with advanced cardiac disease should avoid Hct values in the normal range. In others, Hcts at least up to 39% appear to be safe and effective. Based on this review, a reasonable target Hct range may be 33 to 39%, which balances the risks and potential benefits.

Since recombinant erythropoietin was introduced into clinical practice in 1989 for the treatment of ESRD-related anemia, considerable attention has been spent on determining the appropriate degree of correction of the hemoglobin and the associated clinical benefits. A number of clinical trials have defined the physiologic changes that occur when the hematocrit level is increased from the pre-Epoetin era level of less than 30% to hematocrits of greater than 30%, and more recently, to hematocrits in the higher ranges of 38–42% [1–5]. The clinical benefits of correcting hematocrits to >30% have shown improved exercise capacity, cognitive function, better quality of life, improved cardiac function, and improved sexual function [6–10]. The physiologic improvements have subsequently been tested in prospective clinical trials and observational studies to determine the impact of anemia correction on mortality and the associated morbidity.

In the fall of 1997, the United States National Kidney Foundation published its Dialysis Outcomes Quality Initiative (DOQI) guidelines suggesting a target hemoglobin of 11–12 g/dL (Hct 33–36%) for dialysis patients based on a review of the literature and opinion of the anemia work group. The target level for correcting anemia, which is below that of the normal population, has been suggested by some investigators to be lower than what should be achieved in order to reduce the high mortality in the dialysis population secondary to cardiac disease [11–13]. One study in the literature by Besarab et al has receive considerable attention because it tested the hypothesis that correcting hemodialysis patients' hematocrits from 30% to 42% would reduce mortality and morbidity in patients with cardiac disease. The study was stopped early because the treatment group mortality was not significantly higher than the control group, and that there was little chance that the primary hypothesis of an improved outcome would be achieved with the time remaining in the trial. This study suggested that there may be limits to the level of correction of anemia that should safely be achieved in the dialysis population.

Given the countering views that a normal hematocrit (Hct) should be achieved and also the risks of complete correction of anemia, this article will review the trial data and observational studies to determine what evidence is available to address the safety of Hcts between 33% and 36%, and the 42% of a normal population level.

THE NORMAL HCT TRIAL IN PATIENTS WITH CARDIAC DISEASE

The evidence developed from earlier trials and the observational studies suggested that patients with cardiac disease, particularly those with left ventricular hypertrophy and congestive heart failure, may benefit from a higher Hct in the normal range. Subsequently, Besarab

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et al in 1998 reported on a trial to test the hypothesis that mortality and morbidity would be reduced in patients with New York Heart Association classification heart disease stage I–III when the Hct was increased to 42% compared with a control group with the Hct sustained at 30% [14]. Six hundred fifteen and six hundred eighteen prevalent hemodialysis patients were randomized to the treatment arms of 30% and 42%, respectively. The higher Hct group required significantly more Epoetin and intravenous iron to achieve the higher Hct levels. The primary outcome was time to death or first nonfatal myocardial infarction. Secondary outcomes tracked hospitalizations with detailed categorizations of the principal cause of the admissions. The follow-up period was 29 months, with the study terminated early secondary to a non-significant higher risk of death (RR = 1.30; CI, 0.09–1.90) in the Hct group 42%. This action will be taken since the remaining time in the study would not offset the trends such that the principal hypothesis could not be proven. Therefore, to reduce the potential risk to the study subjects, the trial was stopped. Less than 150 patients (12.1%) had been followed for 24 months when the trial was stopped. Post hoc analysis showed that when the treated patients were divided by Hct level, the normal Hct treatment group had higher death rates even though their achieved Hcts were comparable to the low Hct group. The higher death rate finding continued up to Hct levels of 36–39%; however, those patients that achieved an Hct of 39–41% had a lower death rate. This later observation may represent select and survivor bias and should be viewed with caution.

The unexplained findings of a higher death rate in the normal Hct treatment arm raised concerns that the trial may have had an unrecognized confounding element that was not considered. The higher Hct treatment group resulted in significantly more the intravenous iron being given compared with the control group. The authors suggested that this confounding effect may contribute the reasons for the differences in the outcomes. Unfortunately, the post hoc nature of the analysis could not be used to dismiss the trial findings that the normal Hct group did not benefit with reduced mortality or a morbidity secondary to hospitalizations. The one area of clear finding was related to an increase in vascular access thrombosis in the normal Hct group. These findings were not subjected to the same Hct level analysis as was done in the mortality report, thereby leaving the issue unresolved. Thus, this trial suggested that patients with cardiac disease of NYHA class I–III do not benefit from a Hct of 42% compared with an Hct of 30%. Unfortunately, little else can be gleaned from this study as there appears to be a concern about the use of large doses of IV iron, a suggested risk factor in the general population for cardiac disease. This iron hypothesis has also been questioned as well, but no additional studies have been reported to settle the debate [15–24].

HIGHER HEMATOCRIT LEVELS IN LOW RISK POPULATIONS: IMPACT ON QUALITY OF LIFE AND FUNCTIONAL STATUS

Concerns over the lack of benefit of an increased Hct in patients with cardiac disease led a number of investigators to reevaluate the clinical limits that can be achieved in patients with established heart disease. Moreno et al studied patients without cardiac disease, accessing the impact of increasing Hct levels over a six-month period as reported in 2000 [25]. This multi-center prospective 6 month interventional trial was performed in patients with a mean Hct of 31%, increasing their Hct to 38.5% assessing their Sickness Impact Profile (SIP) and Karnofsky score before and after intervention. One hundred fifteen patients without significant cardiac disease were treated with their initial SIP of 8.9 and, after achieving the higher Hct, the score decreased to 7.25 ($P < 0.001$), an 18.5% improvement. Their functional status also improved from a Karnofsky score initially of 75.6 to 78.4 ($P < 0.01$), a 3.7% improvement. Additional information was presented on their pattern of morbidity from hospitalizations comparing the previous six months' pattern with that noted during the six-month intervention. Total hospitalizations were reduced 58% ($P < 0.05$), and total hospital days decreased 69% ($P < 0.05$). No patient deaths were noted, and only 11 patients dropped out of the study secondary to vascular access thrombosis ($N = 9$, 5.7%) and hypertension ($N = 2$, 2%). This study, in contrast with the Besarab et al study, showed a significant improvement in both morbidity and patient well-being. One possible explanation for these findings may center on the cohort studied. These low risk patients had less established disease that may have lowered the potential risk as the higher Hct levels are achieved. The level of anemia correction was also different in the Moreno et al study, with patients achieving an average of 38.5% compared with the Besarab et al study which targeted a 42% Hct. Another important comparison between the two studies relates to the early deaths. In the Besarab et al normal Hct trial in patients with cardiac disease, approximately 11% of the patients had died or had an acute myocardial infarct within the first six months of the study. In contrast, the Moreno et al trial in patients without cardiac disease had no deaths during the six-month treatment phase. The markedly different hospitalization patterns between the studies at least suggest that Hcts of 38.5% in non-cardiac disease patients are not only safe but also effective at reducing morbidity. This was the first study to demonstrate improved outcomes in patients with an Hct above the DOQI target of 36%.

OBSERVATIONAL STUDIES DEMONSTRATING AN ASSOCIATION BETWEEN HCT LEVELS AND CLINICAL OUTCOMES

In contrast to the above randomized prospective controlled multi-center trial and the prospective interventional study, at least five observational studies have been published showing a lower associated morbidity and mortality when the Hct level was greater than 30% [8, 9, 26–28]. The first study demonstrating this association was published in 1997 by Madore et al. This observational study investigated 18,792 patients who were alive at the end of 1992, with three months of biochemical and Hct data available from October, November, and December 1992, with followup through 1993. Because observational studies must address potential selection bias, the investigator added increasing amounts of clinical data to the logistic regression model odds ratio of death. Three models were run with age, gender, and race only, the previous model with albumin and the final model which added monthly biochemical data and urea reduction ratio. Each of the models gave very similar results, with the highest odds of death occurring in the patients with hemoglobins of ≤80 g/L (OD: 1.5–2.0) compared with those with hemoglobins of 100–110 g/L. The risk decreased to 25% higher at hemoglobins of 90–100 g/L and were not significantly different for those hemoglobins of greater than 110 g/L. The additional case mix and clinical data adjustment only changed the associated risks in the groups with hemoglobins of less than 90 g/L with the others being unchanged [26].

This study supported the hemoglobin range of 100–110 g/L but did not demonstrate any benefit associated with the higher hemoglobin levels above 110 g/L. One concern about this study was the analysis of the patients with hemoglobins above 110 g/L. The payment policies in the United States were restrictive for patients with hemoglobins above 120 g/L such that those patients needed medical indications to justify Epoetin treatment to sustain a higher hemoglobin level. Therefore, not all patients were able to achieve this level of hemoglobin correction in addition to the fact that the higher hemoglobin group may have had more disease. To the extent that the adjustment could address these differences, there was no benefit from a mortality standpoint between the group with a hemoglobin level of 100–110 g/L and those greater than 110 g/L. This study did clearly establish that patients with lower hemoglobins were associated with significant adverse outcomes.

Supporting evidence for the above observational study was subsequently reported by Locatelli et al in 1998 in a report from the Lombardy dialysis registry in northern Italy. In this study, 5,302 prevalent dialysis patients alive on December 31, 1995 were characterized into Hct groups of <27%, 27–32%, and >32%. Explanatory variables included age, gender, co-morbidity, dialysis modality, and prior ESRD time. The outcome was the odds ratio of death in the next year of followup assessed in a logistic regression model. Also, the hospitalization rates and total hospital days were evaluated between the three Hct ranges. Crude mortality was highest at 16% in the Hct group of <27% and was lower at 11% in the Hct group of >32%. Cardiovascular death and cerebrovascular death were also lowest in the group of >32%. Hospitalization days were the lowest on the Hct group of >32% at 11 days compared with 13 days for the group of 27–32% and 16.5 days per patient's year at risk. This study established the lower associated hospitalization risk when the patients Hct was >32% compared with lower levels of anemia correction. The findings of lower cerebral vascular deaths also allayed concerns about the potential risk of hypertension and cerebral vascular events when patients' Hcts were corrected to levels above 30% [27].

Two large national studies from the United States were subsequently published by Ma et al and Xia et al in 1999 which were companion studies on the same cohort of Medicare hemodialysis patients from 1993. These authors first reported mortality associations with the second paper addressing the risk of hospitalization. These investigators evaluated prevalent Medicare hemodialysis patients that survived the period from July 1, 1993 to December 31, 1993, assessing their co-morbidity, history of vascular access procedures, history of blood transfusions, and total hospital days during the six-month entry period. The severity of disease measures were determined to address the concerns that patients with lower Hcts may have a greater degree of co-morbidity that could confound analysis. Hcts were computed for patients who had at least 3 measurements in the six-month entry period to better characterize the stability of the Hct level and whose measurements would be representative of the six-month fixed survival period. All patients were followed for one year assessing the risk of death in a Cox regression model and the risk of multiple hospitalizations using an Anderson-Gill multiple event model. Sensitivity analyses were performed for both studies to determine how many patients would be required in each Hct group in order to achieve a significant result in the higher Hct groups [8, 9].

The risk of first and multiple hospitalizations followed the mortality pattern previously reported by Madore et al and Locatelli et al but differed in that patients with Hcts of 33–36% had a 8% significantly lower risk than patients with Hcts of 30–33%. The sensitivity analysis showed that the higher Hct level results associated with hospitalizations required at least 3500 to 4000 patients in the Hct group of 33–36% in order to determine the significance of risk. The mortality associations by Ma et al were similar to the Madore et al and Locatelli et al

morality studies but showed a 4% lower risk of death at an Hct of 33–36% compared with the Hct group of 30–33%. The sensitivity analysis showed that the mortality findings in the higher Hct group required at least 16,000 patients in that cell in order to achieve significance. The low sensitivity of the mortality event is consistent with all the previous trials including the Besarab et al study which was a randomized trail of 600+ patients in each cell (Hct 30% vs. 42%) which would have been underpowered to show any impact of the higher Hct level in either the mortality event or the hospitalization event. Therefore, conclusions about the impact of higher Hcts are vulnerable to the size of the reported study.

In November 2001 Collins et al published a study of incident Medicare hemodialysis patients from 1996 through June 30, 1998. Each patient survived to month 9 after the ESRD first service date, and their Hct levels were determined in the month 4 to month 9 period of survival. The patients were characterized for co-morbidity, severity of disease, and Hct levels in a manner that was previously used in the Ma et al and Xia et al studies. Followup of the patients was for one year with the outcome being the risk of death or first hospitalization. A Cox regression model was used with adjustments for age, gender, race, diabetes, co-morbidity, severity of disease, and Hct level. The analysis also evaluated the relative cost of Medicare allowable expenditures based on the Hct levels. The findings in this incident population were more definitive than the 1993 prevalent cohort in that the associated risk of death was lowest in the Hct group of 33–36% and was not different in the Hct group of 36–39% or the 39+% groups. Based on the previous sensitivity studies from these authors, the mortality analysis was underpowered to demonstrate any impact on mortality. These findings on mortality are consistent with all the other mortality studies in that there appears to be no difference in this major outcome [28].

The morbidity outcome, however, was adequately powered as over 4000 patients were noted in the Hct group of 36–39%. Here the risk of first hospitalization in the follow-up period was lowest in the Hct group of 36–39%. The Hct group 39+% showed no difference compared with the Hct group of 33–36%, but this group only had 555 patients which were insufficient to draw any conclusions. The financial analysis also showed the group with an Hct of 36–39% was associated with the lowest cost of care, 8% lower than the Hct group of 33–36%, and 32% lower than the patients with Hcts of <30%. Additional finds also showed that the dose of Epoetin was lowest in the Hct groups of 36–39% and 39+% compared with the group of 33–36%. The adjusted dose difference was 26–39% lower than the Hct group of 33–36%. This later observation demonstrated that the higher Hct groups did not require more Epoetin to achieve these levels. The reasons for this observation may be secondary to selection bias in that patients with less co-morbidity and severity of disease may be more responsive to Epoetin and therefore will require lower doses. The study attempted to adjust for these differences; however, these findings should be viewed only as associations and not causal. A more definitive study would require a prospective randomized design to demonstrate the direct relationship.

The latest study on incident patients demonstrating an association between a lower risk of hospitalization in patients with Hcts of 36–39% and no adverse mortality risk compared with patients with Hcts of 33–36% suggests that the concerns raised by the normal Hct trial may be important to reconsider. The clinical reality is that the dialysis population appears to initiate ESRD treatment with an Hct on average of <30% and increase their Hct over a three or four month period toward an Hct at the midpoint of the DOQI range [29]. Few data are available in this early correction phase that mimics the ramp-up phase of the normal Hct trial which showed an increased risk of death in patients with severe cardiac disease. More investigation is needed to determine if the higher Hct levels pose an early risk of death to patients. The observational data and the study by Marone et al would suggest that Hcts of 36–39% may be effective in the hemodialysis population compared with the 33–36% current target. From this standpoint, it may be clinically reasonable to broaden the target range to 33–39%, which would be a more reasonable biologic range based on the variability in a patient's Hct level month to month. It is still prudent to limit the increase in Hcts in Epoetin-treated patients with cardiac disease to below 42% until more definitive studies are performed.

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